



# COVID-19 Pneumonia: When Negative RT-PCR Testing Does Not Rule out the Disease

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## Abstract

In diagnosing COVID-19, false negative findings from the biological sample taken from a mucosal swab of the upper respiratory tract and tested with the real-time reverse-transcription polymerase chain reaction (RT-PCR) technique have been reported. This patient has had a proven contact with an infected person, clear symptoms of viral respiratory disease, yet negative test results on the fifth day of self-isolation. On repeated test after 48 hours, on the 7th day of isolation, due to persistence of some symptoms, he tested positive for SARS-CoV-2. The existence of symptoms and characteristic signs after laboratory and radiological analysis of the patient prompted the repetition of the tests, which at the end led to the confirmed diagnosis and the possibility for adequate treatment of the patient as well.

**Key words:** COVID-19, SARS-CoV-2, pneumonia, false negative RT-PCR.

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## Introduction

COVID-19 represents a disease caused by the novel corona virus (first named 2019-nCoV, later renamed to SARS-CoV-2), which initially emerged in the Chinese town Wuhan, at the end of 2019.<sup>1</sup> It is a case of a new virus from the Coronaviridae family, which was not recorded before, so the clinical features and diagnostics are different from the diseases caused by the already known viruses from this family, severe acute respiratory syndrome (SARS) and Middle-East respiratory syndrome (MERS).<sup>2,3</sup> COVID-19 represents a highly contagious respiratory disease with, in most cases, mild clinical presentation.<sup>4,5</sup> False negative results received from the mucosal swab of the upper respiratory tract and tested with real-time reverse-transcription polymerase chain reaction (RT-PCR), especially in early stages of the disease, have been reported.<sup>6-9</sup>

This is a case report of a patient with symptoms of the upper respiratory tract infection who had initially tested negative for COVID-19 on the fifth day of self-isolation and then positively when the test was repeated two days later.

## Case history

A male patient, aged 62, contacted the medical authorities by phone because of the symptoms that included mild dry cough, slightly increased body temperature (37.5 °C), languor, subjective feeling of shortness of breath and loss of senses of smell and taste. Previous health problems like long-lasting diabetes treated with oral hypoglycaemic agents were revealed from the patient's medical history. He was a non-smoker, overweight (BMI = 28.3 kg/m<sup>2</sup>) and moderately physically active.

The symptoms appeared on the third day of self-isolation that he started when his son tested positive for SARS-CoV-2. On the fifth day of self-isolation, on 23 March 2020, he was admitted to the Department of Infectious Diseases, General Hospital Doboj, after which a nose swab was taken from him and sent for further testing to Banja Luka University Clinical Centre of the Republic of Srpska (BL-UCCRS). The RT-PCR method then showed that the test had been negative. The patient was taken back home to continue his self-isolation.

During the next two days, his body temperature fell to normal values during the day but it kept rising to 37.5 °C in the evening. His cough was less frequent, but the feeling of shortness of breath persisted and the patient was driven to a medical institution on 25 March. It has been ascertained by observation that the patient is conscious, oriented and eupnoeic while sitting in the upright position. Physical examination revealed: on lung auscultation exaggerated, but symmetrical vesicular breathing sounds, mild hyperaemia of the throat and normal blood pressure. The tests that were performed were complete blood count, sedimentation of erythrocytes (SE), C-reactive protein (CRP), pulse oximetry, electrocardiogram (ECG)

and posteroanterior roentgenogram (X-ray) of the lungs.

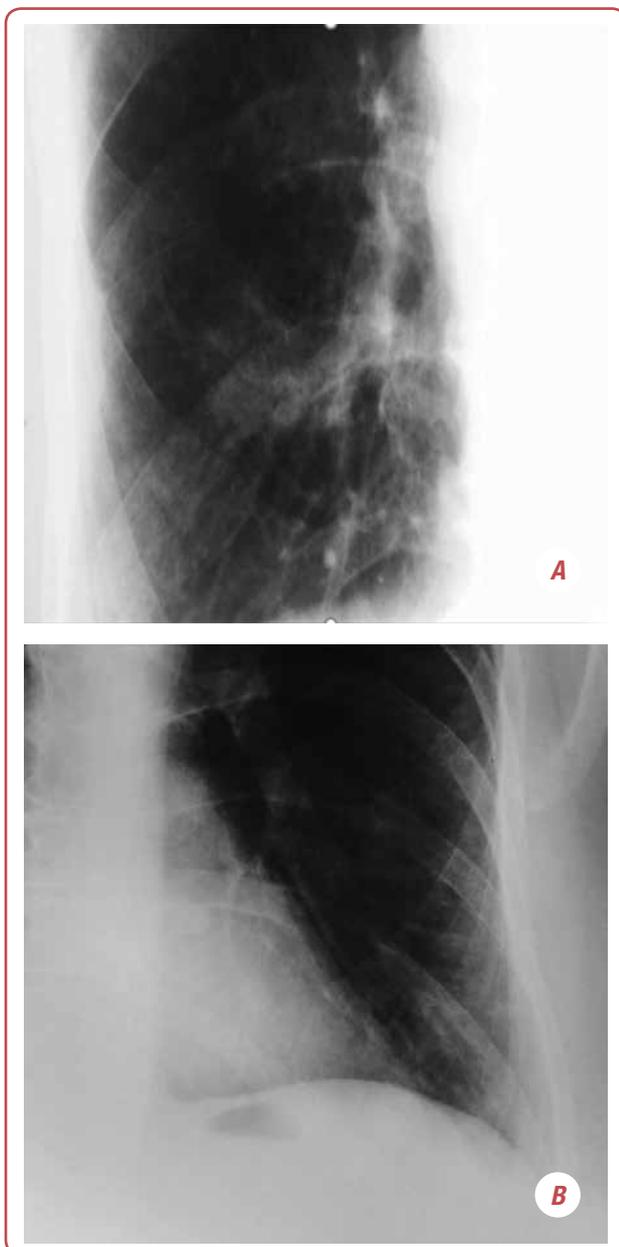
Complete blood count revealed a lymphopenia, with normal values of the leukocytes, erythrocytes and thrombocytes. SE was 68 mm after 30 minutes, the value of CRP was 75.6 mg/L. Pulse oximetry showed a lower oxygen saturation (SaO<sub>2</sub>) of 81 %. The ECG showed sinus tachycardia, with the heart rate of 105 per minute, with left axis deviation, expressed muscle artefact and ST segment in the isoelectric line. On the posteroanterior chest X-ray, the following was observed: oval inhomogeneous opacity in the middle third of the right lung wing of peripheral localisations with accentuated hilar shadows. Basal left part showed a shadowing in the lower third section with the shadowing of the costophrenic angle. Interlobar pleural effusion was noticed on the right (Figure 1).

All of these findings suggest that this is the case of bilateral pneumonia, most likely due to viral aetiology, in a patient that was in direct contact with a person that was suffering from COVID-19 and who tested negative two days before this examination, on the fifth day after contact.

The patient was sent to be re-tested and he was admitted to the Infectious Disease Clinic of the BL\_UCCRS, on the same day, ie on the 7th day after contact with SARS CoV-2-infected person. The repeated test was positive for SARS-CoV-2 and a definitive diagnosis of a bilateral bronchopneumonia was established. The patient was hospitalised for additional ten days with moderately severe clinical manifestations of the disease and was treated with hydroxychloroquine tablets according to treatment guidelines for COVID-19 infection.

## Discussion

Currently, the RT-PCR method of detection of viral ribonucleic acid (RNA) in the respiratory tract is the gold standard in diagnosing COVID-19.<sup>10</sup> The swab from the upper respiratory tract mucosa is taken most frequently, but it is recommended to take the sample from the lower respiratory tract whenever possible.<sup>7</sup> RT-PCR has high specificity, but its sensitivity is between 60 and 70 %, which requires retesting in up to 30 % of the cases.<sup>11</sup> Our patient with the negative test result on the 5th day of isolation and with present identical symptoms of shortness of breath like on the 7th day when he



**Figure 1.** Chest X-ray of patient with COVID-19-induced pneumonia: (A) Right lung with ground glass opacities, with accentuated hilar shadows. (B) Left lung with basal consolidation.

was retested (this time positively), points out to the need of radiologic and laboratory evaluation in parallel with the PCR processing. Several individual or group case reports have been recorded where the patients had false negative results, very similarly to the patient in this case report.<sup>12,13</sup> The experience so far points to the fact that negative test results of SARS-CoV-2 do not completely exclude the disease.<sup>13</sup>

Alongside this method, laboratory parameters and radiological techniques, predominantly lung computerised tomography (CT) scan, are additionally used to establish the diagnosis.<sup>14</sup> On computerised tomography, changes in lungs induced by COVID-19 are presented in the form of ground glass opacities, spread along the lung parenchyma (medial, lateral and posterior lung fields), localised predominantly peripherally, with the central axis parallel with the pleura.<sup>15,16</sup> In some cases pleural effusion was present as well.<sup>16</sup> In absence of a CT scanner, this patient underwent a postero-anterior chest X-ray, which was in correlation with the global data on radiological presentation of the COVID-19-induced lung lesions.<sup>17</sup>

Regarding the laboratory diagnostics, in patients suffering from COVID-19, lymphopenia was noticed, as well as a negative correlation between the lymphocytopenia and the degree of tissue damage.<sup>18,19</sup> CRP and SE, as inflammatory parameters were increased.<sup>18</sup> It was the case with this patient as well, who had a confirmed COVID-19 pneumonia, lymphopenia with normal values of total leucocytes, accompanied with the increased values of CRP and SE.

In this case report, we presented a patient who was in direct contact with a SARS-CoV-2- infected person for a longer time period, after which he developed symptoms of a febrile respiratory tract infection. This was the indication for testing.<sup>7</sup> First testing was done without radiological and laboratory processing on the fifth day after contact. RT-PCR showed negative test results, which is relatively common in the early stage of the disease (RT-PCR sensitivity is 60-70 %).<sup>11</sup> Due to the persistence of symptoms, the test was repeated two days later, after noticeable radiological and laboratory abnormalities had been discovered. This time the patient tested positive for SARS-CoV-2.

At the time of writing this article, there were 8 out of 710 hospitalised patients at the Infectious Disease Clinic of BL-UCCRS having clear clinical manifestations of COVID-19 pneumonia, but with false negative RT-PCR test. Although they have been regularly retested the SARS-CoV-2 infection was

never confirmed in these patients. In many cases, the time of exposure to virus infection is unknown and testing is usually based on time of symptom onset. According to some recent findings, the false negative rate is lowest 3 days after onset of symptoms, or approximately 8 days after exposure to infected patients.<sup>20</sup> Before or after that period the false negative rate is higher and clinicians should be aware of it. It is clear that serial testing would certainly reduce the frequency of false negative results.

## Conclusion

The interpretation of RT-PCR tests for SARS-CoV-2 infection must be taken with caution, particularly at early course of infection. The infection should not be ruled out on the basis of RT-PCR testing alone. It is necessary to perform radiological and laboratory processing of every patient suspected to COVID-19 infection, no matter the results of the RT-PCR testing. Due to low sensitivity of RT-PCR testing, persistence or impairment of clinical features should lead to re-testing.

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## Conflict of interest

None.

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